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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/573,131	04/18/2006	Darrel W. Stafford	5470-401	4529
20792 7590 05/31/2007 MYERS BIGEL SIBLEY & SAJOVEC PO BOX 37428 RALEIGH, NC 27627			EXAMINER SITTON, JEHANNE SOUAYA	
			ART UNIT 1634	PAPER NUMBER
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/573,131	Applicant(s) STAFFORD ET AL.	
	Examiner Jehanne S. Sitton	Art Unit 1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 02 March 2007.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-5 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-5 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date <u>4/07, 4/07, 3/07, 7/06</u> | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Election/Restrictions

1. Applicant's election of Group I, claims 1-5, was made **without** traverse in the reply filed 3/2/2007. Claims 6-16 have been canceled. An office action on the merits of claims 1-5 follows.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 1-5 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. There are many factors to be considered when determining whether there is sufficient evidence to support determination that a disclosure does not satisfy the enablement requirements and whether any necessary experimentation is undue. These factors have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

“Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in *Ex parte Forman*. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.”

Art Unit: 1634

It is noted, that although the specification is silent with regard to population based studies, the specification and the art is enabling for a method of screening for a single nucleotide polymorphism in the VKOR gene of a human subject which is associated with increased sensitivity to warfarin, comprising detecting single nucleotide polymorphisms in the VKOR gene of a human subject, performing a population based study to detect the polymorphisms in a group of human subjects with increased sensitivity to warfarin and ethnically matched controls, identifying an allele of a single nucleotide polymorphism in the VKOR gene which is associated with increased sensitivity to warfarin.

The nature of the invention and the breadth of the claims:

The claims (1-3) are broadly drawn to methods of identifying a human subject having an increased sensitivity to warfarin by detecting in any human subject, of any ethnicity (such as Asian, Caucasian, African, African American, and Hispanic), the presence of a single nucleotide polymorphism in the VKOR gene, wherein the single nucleotide polymorphism is correlated with increased sensitivity to warfarin, thereby identifying the subject as having an increased sensitivity to warfarin. The claims are further drawn to the single nucleotide polymorphism G to C at nucleotide 2581 of SEQ ID NO: 11.

The claims therefore require a predictive association between any single nucleotide polymorphism in the VKOR gene (VKORC1) and warfarin sensitivity, in any human subject.

The claims (4-5) are also drawn to identifying a single nucleotide polymorphism in the VKOR gene correlated with increased sensitivity to warfarin or correlating a SNP in the VKOR gene of a subject with increased sensitivity to warfarin by identifying a human subject having

Art Unit: 1634

increased sensitivity to warfarin, detecting a SNP in the in the VKOR gene of the subject, and correlating the presence of a single nucleotide polymorphism in the VKOR gene with increased sensitivity to warfarin in the subject. The claims therefore require a predictive association between a SNP in the VKOR gene identified in a single subject, and increased sensitivity to warfarin.

The invention is in a class of inventions which the CAFC has characterized as 'the unpredictable arts such as chemistry and biology' (Mycolgen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Federal Circuit 2001)).

The amount of direction or guidance and Presence and absence of working examples:

The specification teaches that a subject with “increased sensitivity to warfarin” is a subject for whom a suitable therapeutic or maintenance dose of warfarin is lower than the dose suitable for a “normal” subject, that is a subject who does not carry the SNP (page 15). The specification teaches that three mutations were identified in the VKOR gene: vk2581 G to C, vk3294 T to C, and vk4769 G to A, and were examined for a correlation between their presence in a subject and the maintenance dose of warfarin required to achieve a therapeutically effective response. The specification teaches that of the subjects studied, the average warfarin dose for patients (26) with the vk2581 G allele was 50.19 +/- 3.2 mg per week, while those heterozygous (17) and homozygous (15) for the C allele were 35.19 +/- 3.73 and 31.14 +/- 6.2 mg per week, respectively (page 21). The specification also teaches average warfarin doses for patients with the vk3294 and vk4769 polymorphisms (page 21, figures 1B and 1C). However, the specification is silent with regard to analyzing whether such an association was found across

Art Unit: 1634

different races or ethnicities of human subjects. Additionally, the claims broadly encompass the association between warfarin sensitivity by analyzing any single nucleotide polymorphism in the VKOR gene. Geisen (Geisen et al; Thromb Haemost. Vol 94, pages 773-779. 2005) teaches that there are over 25 SNPs in the VKOR gene (see table 1). However the specification is silent as to an association between these particular SNPs and warfarin sensitivity. The claims broadly encompass the investigation of a broad scope of possible genomic regions for alleles which are indicative of warfarin sensitivity. However, the specification provides no correlation between the identity of broadly any SNPs, that is their structure, with the function or phenotype of warfarin sensitivity. Therefore, the skilled artisan would be unable to predictably correlate any other structural change in any other region of VKORC1, and warfarin sensitivity.

Additionally, claims 4-5 encompass methods where correlations to warfarin sensitivity are made by analyzing a single subject. However, in such a situation, the presence of a particular allele of a SNP in VKOR and warfarin sensitivity could not be predictably established as it would not be known if the presence of the allele were due to chance or was actually associated with warfarin sensitivity.

The state of the prior art and the predictability or unpredictability of the art:

The unpredictability in the associated technology is high. There is a large body of knowledge in the prior art related to polymorphisms in general, and their association with diseases or disease states. However, the art is highly unpredictable with regard to the functionality of polymorphic sites in genomic DNA. After a screening assay identifies polymorphisms, it is unpredictable whether any such polymorphisms would be associated with

Art Unit: 1634

any phenotypic trait, such as a disease state, a physiological state, or drug metabolism or response. For example, Hacker (Hacker et al; Gut, 1997, Vol. 40, pages 623-627) teaches that they were unable to confirm an association between a gene polymorphism and ulcerative colitis in a case where prior studies suggested such a relationship would exist since the relationship had been identified in a different population. Even in cases where an association between a particular gene and a disease state is known to exist, such as with the LPL gene and heart disease risk or the p-globin gene and sickle cell anemia, researchers have found that when using SNP (single nucleotide polymorphism analysis) it was difficult to associate SNPs with disease states or to even identify key genes as being associated with disease (Pennisi, Science, 1998; 281; 1787-1789).

With regard to VKOR polymorphisms, the identity of the nucleotide at position 2581 of SEQ ID NO 11, does not appear to be as predictably associated with warfarin sensitivity in any human population. For example, in table 2 of Reider (Reider et al; US Pregrant publication 2006/0084070), it can be seen that haplotype 3 contains a C at position 6853 (corresponds to position 2581 of SEQ ID NO: 11). However this haplotype is found in a number of African controls. Geisen teaches that warfarin sensitivity is known to vary between different ethnicities and that there is a significantly higher average warfarin requirement in subjects of African American ethnicity (page 778, coo. 1, 2nd full para). This teaching appears at opposite with the broad assertions set forth in the claims as the identify of the SNP at position 2581 would not appear to be predictive of warfarin sensitivity in this population. Additionally, as can be seen from the haplotypes in table 1 of Reider, a number of particular alleles of SNPs in VKOR are found in subjects who have warfarin sensitivity and warfarin resistance. Accordingly, it appears

Art Unit: 1634

that not all SNPs would be predictive of warfarin sensitivity based on the finding that it was found in a single subject with warfarin sensitivity, particularly given the art acknowledged inter-individual and inter-ethnic variability in warfarin sensitivity (see Geisen and Reider).

The level of skill in the art:

The level of skill in the art is deemed to be high.

The quantity of experimentation necessary:

Although the level of skill in the art is high, the unpredictability of associating polymorphisms with phenotypic traits is even higher. To practice the invention as broadly as it is claimed, the skilled artisan would have to perform a large study of cases and controls in different human populations to determine whether the C at position 2581 of SEQ ID NO: 11 was predictably associates with warfarin sensitivity as well as characterize additional sequences within the VKORC1 gene and determine if they are predictably associated with warfarin sensitivity, as well as determining whether the polymorphisms are so associated in any population or whether the association is population specific. Given the unpredictability in the associated technology, this experimentation would be replete with trial and error experimentation, with the results of each analysis being unpredictable. Such experimentation is considered undue.

Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the absence of a working example

Art Unit: 1634

and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

4. Claims 1 and 3-5 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are broadly drawn to methods of identifying a human subject having an increased sensitivity to warfarin by detecting in any human subject, the presence of a single nucleotide polymorphism in the VKOR gene, wherein the single nucleotide polymorphism is correlated with increased sensitivity to warfarin, thereby identifying the subject as having an increased sensitivity to warfarin. The claims are also drawn to identifying a single nucleotide polymorphism in the VKOR gene correlated with increased sensitivity to warfarin or correlating a SNP in the VKOR gene of a subject with increased sensitivity to warfarin by identifying a human subject having increased sensitivity to warfarin, detecting a SNP in the in the VKOR gene of the subject, and correlating the presence of a single nucleotide polymorphism in the VKOR gene with increased sensitivity to warfarin in the subject.

The claims therefore encompass a large genus of single nucleotide variants, including deletions, substitutions, and insertions at any site within the VKORC1 gene. This genus

Art Unit: 1634

includes a large number of polymorphisms and mutations for which no written description is provided in the specification. This large genus is represented in the specification by only the particularly named 3 polymorphisms for which data is provided. This data, however, does not provide for a predictable association between any single nucleotide polymorphism in VKORC1 and warfarin sensitivity, as is broadly claimed. Here, no common element or attributes of the sequences are disclosed which would permit selection of sequences as polymorphisms. No structural limitations or requirements which provide guidance on the identification of sequences which meet these functional limitations of associating a polymorphism with warfarin sensitivity is provided. Further, although the specification teaches that the SNPs in intron 2 and the 3' UTR are linked, as evidenced by the teachings of Reider (US Pregrant Publication 2006/0084070), the polymorphisms in intron 2 and the 3' UTR are not necessarily predictably indicative of each other (see Tables 1 and 2, the last three SNPS taught by Reider correspond to the SNPs at position 2581, 3294, and 4769 of instant SEQ ID NO: 11).

The claims broadly encompass the investigation of a broad scope of possible genomic regions for alleles which are indicative of warfarin sensitivity. However, the specification provides no correlation between the identity of broadly any SNPs, that is their structure, with the function or phenotype of warfarin sensitivity. Therefore, the skilled artisan would be unable to predictably correlate any other structural change in any other region of VKORC1, and warfarin sensitivity.

The individual polymorphisms set forth in the specification are not representative of the genus of any polymorphism associated with warfarin sensitivity, because it is not clear which polymorphisms within the broad region encompassed by the claims would have the same affect.

In analysis of the claims for compliance with the written description requirement of 35 U.S.C. 112, first paragraph, the written description guidelines note regarding genus/species situations that "Satisfactory disclosure of a ``representative number" depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed." (See: Federal Register: December 21, 1999 (Volume 64, Number 244), revised guidelines for written description.) In the instant case, the specification fails to teach the necessary common attributes or features of the genus of encompassed nucleic acids and polymorphisms in view of the species disclosed. As such, one of skill in the art would not recognize that applicant was in possession of the genus of nucleic acids and polymorphisms encompassed by the broadly claimed invention.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

The skilled artisan cannot envision the detailed chemical structure of the encompassed nucleic acids and polymorphisms, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The nucleic acid itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993), and Amgen Inc. V. Chugai

Art Unit: 1634

Pharmaceutical Co. Ltd., 18 USPQ2d 1016. The current situation is a definition of the compound solely based on its functional utility, as a polymorphism, without any definition of the particular polymorphisms claimed.

Finally, *University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398, 1404, 1405 held that:

To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); *In re Gosteli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) ("[T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." *Lockwood*, 107 F.3d at 1572, 41 USPQ2d at 1966.

An adequate written description of a DNA, such as the cDNA of the recombinant plasmids and microorganisms of the '525 patent, "requires a precise definition, such as by structure, formula, chemical name, or physical properties," not a mere wish or plan for obtaining the claimed chemical invention. *Fiers v. Revel*, 984 F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993). Accordingly, "an adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself." *Id.* at 1170, 25 USPQ2d at 1606.

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Art Unit: 1634

6. Claims 1 and 3-5 are rejected under 35 U.S.C. 102(e) as being anticipated by Oldenburg (Oldenburg et al; US Pregrant publication 2005/0271644).

Oldenburg teaches a method of determining polymorphisms in the VKORC1 gene (see para 0168, 0170, 0171 and example 8), associated with warfarin sensitivity. With regard to claims 1 and 3, it is noted that although Oldenburg teaches specific mutations subjects with warfarin resistance, the term “increased sensitivity to warfarin” is a relative term and depends on the comparison. Individuals with a C at position 292 are more sensitive to warfarin than individuals with a T. With regard to claims 4 and 5, Oldenburg teaches identifying sensitive rats (example 9), detecting nucleotide polymorphisms in the subject and correlating the presence of the polymorphism with warfarin sensitivity.

7. Claims 1 and 3-5 are rejected under 35 U.S.C. 102(a) as being anticipated by Rost (Rost et al; Nature vol. 427, pages 537-541 February 5, 2004).

Rost teaches a method of determining polymorphisms in the VKORC1 gene (see abstract, page 537, col 2), associated with warfarin sensitivity. With regard to claims 1 and 3, it is noted that although Rost teaches specific mutations found in patients with warfarin resistance, the term “increased sensitivity to warfarin” is a relative term and depends on the comparison. Individuals with a C at position 292 are more sensitive to warfarin than individuals with a T. With regard to claims 4 and 5, Rost teaches identifying sensitive rats (col. 2, para 4), detecting nucleotide polymorphisms in the subject and correlating the presence of the polymorphism with warfarin sensitivity.

Art Unit: 1634

Conclusion


8. No claims are allowable.
9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jehanne Sitton whose telephone number is (571) 272-0752. The examiner can normally be reached Monday-Thursday from 8:00 AM to 5:00 PM and on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached on (571) 272-0735. The fax phone number for this Group is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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Jehanne Sitton
Primary Examiner
Art Unit 1634

5/22/07